High-sensitivity C-reactive Protein is Predictive of Medium-term Cardiac Outcome in High-risk Asian Patients Presenting With Chest Pain Syndrome Without Myocardial Infarction

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Abstract

Introduction: High-sensitivity C-reactive protein (hs-CRP) has been shown to be predictive of cardiac events but data among Asians is comparatively few. We evaluated the role of hs-CRP in the prediction of adverse cardiac outcome in a cohort of high-risk patients presenting with chest pain syndrome without myocardial infarction (MI). Materials and Methods: Three hundred and forty-seven patients were prospectively recruited over an 18-month period and patients with MI as documented by serial electrocardiogram abnormalities, and creatinine kinase or troponin elevation were excluded. Mean follow-up duration was 901 ± 306 days. Kaplan-Meier and Cox proportional hazards modelling were used to evaluate outcome and determine association with predictor variables. Results: The composite primary endpoint of cardiac mortality, non-fatal MI, cardiac failure or coronary revascularisation procedure (coronary artery bypass grafting or angioplasty) unrelated to the index admission was reached in 37 patients. History of previous MI (P = 0.002), presence of at least 1 coronary artery with ≥50% stenosis (P = 0.028) and elevated hs-CRP levels were associated with an adverse cardiac outcome (P = 0.001 for CRP in the upper quartile, and 0.002 for CRP ≥1mg/L, respectively). None of the traditional cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, significant family history, smoking, male gender and increased age) was predictive. Multivariate modelling showed elevated hs-CRP to confer the highest risk for an adverse cardiac outcome (P <0.001). Conclusion: Hs-CRP is useful in further stratifying high-risk multi-ethnic patients presenting with chest pain despite no evidence of MI. Close follow-up and aggressive management of these patients may be warranted.

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Introduction

Patients with chest pain often pose a diagnostic conundrum to the attending physician especially when symptoms are not typical of angina and the electrocardiogram non-diagnostic.[1] Troponin levels are frequently measured at presentation to prognosticate the patient. Because elevated levels of troponin indicate myocardial necrosis, they may not be elevated acutely despite an unstable situation. Physicians have therefore been searching for more sensitive biochemical markers for an unstable patient. With recent studies showing atherosclerosis to be an inflammatory disease, markers of inflammation have been increasingly advocated.[2] Amongst these markers, high-sensitivity C-reactive protein (hs-CRP) has been gaining popularity because of easy assay availability, biochemical stability, international standards and inter-assay precision.[3] Elevated levels of hs-CRP predict an adverse outcome in patients presenting with stable and unstable angina pectoris,[4-12] and have also been shown to be predictive of an adverse outcome among patients with chest pain even in the absence of biochemical markers of myocardial necrosis.[6,13-15] Most studies, however, have included patients

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with myocardial infarction (MI) and current data are derived from a predominantly Caucasian population. Because of possible confounding from associated MI, we sought to study the predictive value of hs-CRP in a group of patients with chest pain but without MI. Additionally, we also wanted to determine if the current threshold value of CRP level indicating a low-risk profile is applicable to the local multi-ethnic Asian population.

Materials and Methods

This is a prospective, longitudinal study evaluating the outcome of a cohort of patients admitted to the National University Hospital of Singapore from June 1999 to December 2000 for chest pain complaint requiring coronary angiography. All patients were assessed to be of at least intermediate risk of having significant coronary artery disease (CAD) based on clinical assessment or a recent (within 2 weeks) abnormal stress test (exercise treadmill, dobutamine stress echocardiography or nuclear stress imaging). As acute MI is known to elevate CRP levels, patients with evidence of myocardial necrosis were excluded; this was defined by elevated creatine kinase (CK) or troponin on serial monitoring. We also excluded patients with cardiac failure. The presence of co-morbid inflammatory diseases known to be associated with elevation of CRP, such as rheumatoid arthritis, malignancies, infection or inflammatory bowel disease, also served as exclusion criteria. The study protocol was approved by our institution ethics committee and written informed consent was obtained from all subjects prior recruitment.

Clinical Data

Baseline clinical characteristics including demographic and clinical data were obtained at enrolment. Details of clinical presentation and inpatient management were documented. Ongoing smokers and those who have stopped smoking less than 6 weeks were considered current smokers. All others were grouped as non-smokers for this study. Classic angina was defined as retrosternal chest discomfort exacerbated by exertion and relieved with rest or nitroglycerin. Significant CAD during coronary angiography was identified by at least 50% stenosis in 1 or more major coronary arteries.

Blood Sampling and Biochemical Analysis

In addition to blood samples taken for routine analysis prior to coronary angiography, CK and troponin elevations were also determined on arrival and serially every 8 hours for 24 hours. Coronary angiography was performed as an elective or semi-elective procedure for all patients and fasting (≥8 hours) blood samples were obtained for lipid profile and hs-CRP measurements during arterial puncture. The blood specimen was first stored in ice and transferred to a core lab where the serum was separated and stored at –80°C for subsequent analysis in a single setting. Hs-CRP level was measured using near infrared particle immunoassay (Beckman Coulter, Inc, USA). Analytic sensitivity was 0.2 mg/L and reproducibility was 3.8% to 5.2% for the concentration range of 0.079 mg/L to 3.9 mg/L.

Follow-up

Patients were followed up to June 2003. The primary endpoint was a composite of cardiac mortality, non-fatal MI, cardiac failure or coronary revascularisation procedure (coronary artery bypass grafting or angioplasty). MI was diagnosed if at least 2 of the following criteria were present: (1) cardiac chest pain lasting at least 30 minutes; (2) ≥1 mm ST elevation in at least 2 contiguous ECG leads; (3) CK elevation greater than twice upper limit normal.

Statistical Methods

Continuous variables were presented as means and standard deviations. As the distribution of CRP was highly skewed, logarithmic transformation of CRP was used for statistical analysis. CRP levels were reported as untransformed values. Categorical variables were analysed using a Chi-square test. Survival analysis was performed using the Kaplan-Meier method and differences in mean survival were compared using the log-rank test. The association between individual variables and future outcome was estimated using uni- and multivariate Cox proportional hazards regression models. All statistical testing was 2-sided. Results were considered statistically significant at a level of $P < 0.05$. Data were compiled and analysed in MS Excel 2000 (Microsoft Office 2000, Redmond, WA, USA), and Intercooled Stata 8.0 (Stata Corp, College Station, TX, USA).

Results

Baseline parameters are shown in Table 1. These were patients assessed to be high risk for an unstable coronary syndrome and all underwent coronary angiography in the index admission. The mean (± SD) age of the 347 patients was 58 ± 11 years with a male predominance (65.4%). Two or more cardiovascular risk factors were present in 90.4% of patients. The single most common cardiovascular risk factor was systemic hypertension followed by dyslipidaemia. Diabetes mellitus was present in 37.2%. Previous MI was documented in 16.5% and almost a quarter (21.7%) had a history of coronary artery bypass grafting (CABG) or angioplasty. A total of 171 patients underwent stress testing (exercise treadmill, dobutamine stress echocardiography or nuclear imaging) prior to coronary angiography and 151 patients tested positive. The remaining 20 patients nonetheless proceeded to coronary angiography because of an inconclusive test or progressive

Table 1. Baseline Clinical and Biochemical Profile of Patients

	No. (%)	
Total number of patients in cohort	347	
Chinese ethnicity	218	(62.8)
Malay ethnicity	49	(14.1)
Indian ethnicity	72	(20.8)
Other ethnicity	8	(2.3)
Age ≥65 years	108	(31.1)
Male gender	227	(65.4)
History of previous MI	57	(16.5)
History of previous CABG	22	(6.4)
History of previous angioplasty	53	(15.3)
Diabetes mellitus	129	(37.2)
Hypertension	210	(60.5)
Dyslipidaemia	164	(47.3)
Current smoker	150	(44.0)
Significant family history	64	(18.4)
Classic angina on presentation	240	(69.2)
Positive stress test	151/171	(88.3)
CRP ≥upper quartile	86	(24.8)
CRP ≥1 mg/L	67	(19.3)
≥1 coronary artery with ≥50% narrowing	245	(70.6)

CABG: coronary artery bypass grafting; CRP: C-reactive protein; MI: myocardial infarction

Stress tests include the following: exercise treadmill, dobutamine stress echocardiography and nuclear imaging. A total of 171 patients (49.3%) in the cohort underwent stress testing prior to coronary angiography.

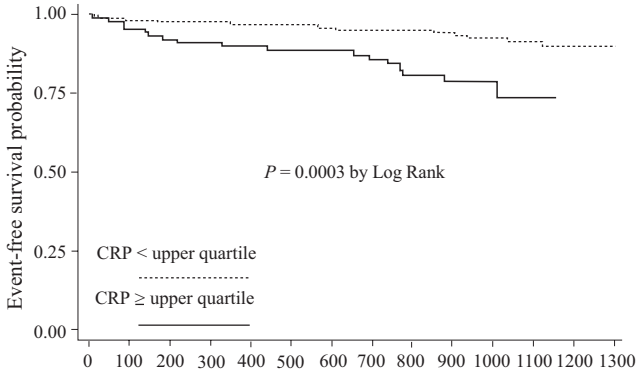

Fig. 1A.

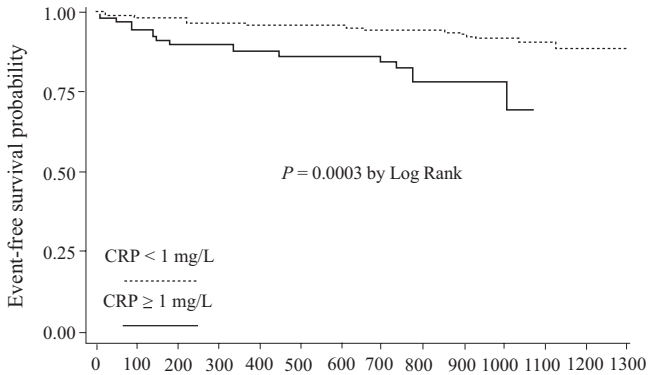

Fig. 1B.

Fig. 1. Survival analysis for CRP levels in the upper quartile (A), and ≥1.0 mg/L (B), and the risk of cardiac mortality, non-fatal myocardial infarction, cardiac failure, or coronary revascularisation during follow-up.

symptoms. Forty-nine patients required revascularisation in the index admission; these were 45 CABG procedures and 4 coronary angioplasties. 99.4% of the patient cohort had follow-up of at least 1 year. Mean follow-up duration was 901 ± 306 days.

Four patients in the initial recruitment had CRP values ≥10.0 mg/L and these were excluded in the analysis despite no obvious source of infection or inflammation. This is in accordance with recommendations made in a position paper by the American Heart Association.[3] The remaining 347 patients do not include these patients. As current reference levels of hs-CRP are derived predominantly from white North American and European populations and no data are available for Asian patients, we empirically defined a "high" CRP level as the highest quartile in this patient cohort (≥0.772 mg/L). We also analysed our results based on currently published data on low risk, defined as a hs-CRP level <1.0 mg/L.[3] Sixty-seven patients had CRP levels ≥1.0 mg/L.

A total of 37 endpoints occurred during follow-up. Eighteen events (48.6%) occurred within the first year. Patients with elevated CRP levels had significantly lower rates of event-free survival (Fig. 1; $P = 0.0003$ for a CRP level in both the upper quartile and CRP ≥1.0 mg/L).

Univariate analysis identified a history of previous MI, presence of at least 1 coronary artery with ≥50% stenosis and elevated CRP levels to be correlated with an adverse outcome (Table 2). Both CRP level in the upper quartile and ≥1.0 mg/L were significant. Among the traditional cardiovascular risk factors, only diabetes mellitus trended to an adverse outcome but this did not achieve statistical significance. Using a Cox proportional hazards model, history of previous MI and elevated CRP levels remained significant on multivariate testing (Table 3). The highest risk ratio, however, was obtained with elevated CRP levels. This was similar for a CRP level in the upper quartile or ≥1.0 mg/L.

When the 49 patients who had revascularisation in the index admission were considered alone, none were noted to have a primary outcome. When we excluded these 49 and considered only the remaining 298 subjects, patients with an adverse outcome still had significantly higher CRP levels (45.9% vs 21.8%, $P = 0.001$ for CRP in the upper quartile; and 37.8% vs 16.5%, $P = 0.002$ for CRP ≥1 mg/L). When subjects with significant CAD were compared with those without, CRP levels were not dissimilar (25.3% vs 23.9% for CRP in the upper quartile, $P = 0.786$;

Table 2. Univariate Analysis of Clinical and CRP Levels and the Risk of Cardiac Mortality, Non-fatal Myocardial Infarction, Cardiac Failure or Coronary Revascularisation during Follow-up

Predictor	Risk ratio	Confidence interval	*P* value
Age ≥65 years	1.652	0.855-3.194	0.143
Male gender	1.150	0.577-2.290	0.690
History of previous MI	3.216	1.627-6.360	0.002
History of previous CABG	2.091	0.738-5.925	0.206
History of previous angioplasty	0.964	0.374-2.484	0.939
Diabetes mellitus	1.833	0.961-3.495	0.067
Hypertension	1.225	0.623-2.407	0.552
Dyslipidaemia	1.014	0.531-1.936	0.967
Current smoker	1.554	0.799-3.023	0.193
Significant family history	0.849	0.354-2.035	0.708
Classic angina	1.680	0.768-3.677	0.174
Abnormal stress test	0.592	0.122-2.874	0.537
≥1 coronary artery with ≥50% narrowing	2.451	1.020-5.889	0.028
CRP ≥upper quartile	3.100	1.618-5.941	0.001
CRP ≥1 mg/L	3.188	1.632-6.227	0.002

CABG: coronary artery bypass grafting; CRP: C-reactive protein; MI: myocardial infarction

Table 3. Independent Predictors of Cardiac Mortality, Non-fatal Myocardial Infarction, Cardiac Failure, or Coronary Revascularisation during Follow-up

a. Results of Cox regression analysis using significant univariate predictors and CRP in the upper quartile

Predictor	Risk ratio	Confidence interval	*P* value
History of previous MI	2.891	1.447-5.775	0.003
≥1 coronary artery with ≥50% narrowing	2.100	0.861-5.122	0.103
CRP ≥upper quartile	3.374	1.740-6.541	<0.001

b. Results of Cox regression analysis using significant univariate predictors and CRP ≥1 mg/L

Predictor	Risk ratio	Confidence interval	*P* value
History of previous MI	2.889	1.444-5.780	0.003
≥1 coronary artery with ≥50% narrowing	2.084	0.853-5.091	0.107
CRP ≥1 mg/L	3.466	1.756-6.843	<0.001

19.7% vs 18.3% for CRP ≥1 mg/L, $P = 0.759$).

Of interest is the finding that subjects with Indian ethnicity have higher CRP levels (34.7% vs 21.1% for Chinese, 26.5% for Malays, 25.0% for others, $P = 0.140$ for CRP in the upper quartile; and 27.8% vs 15.6% for Chinese, 22.4% for Malays, 25.0% for others, $P = 0.126$ for CRP ≥1 mg/L). When Indian ethnicity was compared to a composite of all other ethnicities, the difference was significant (34.7% vs 22.2%, $P = 0.028$ for CRP in the upper quartile; and 27.8% vs 17.1%, $P = 0.041$ for CRP ≥1 mg/L).

Discussion

Our study suggests that hs-CRP levels can be used to further risk-stratify CK/troponin negative patients presenting with chest pain syndrome. It also shows that the current cut-point of low risk is appropriate in a multi-ethnic Asian population. There was no significant difference in our results when either cut-point was used. Risk of an adverse cardiac outcome was significantly higher among patients with elevated CRP levels.

Many studies have shown that a low level of hs-CRP among patients presenting with chest pain syndrome is useful in identifying patients with the lowest rate of clinical events during follow-up.[15-18] These studies, however, have included patients with elevated troponin levels, a marker of myocardial necrosis. Myocardial necrosis is known to induce an acute phase reaction which may account for some of the elevation of CRP depending on the time of blood sampling and may therefore bias the result.[19] In our study, myocardial necrosis was excluded by serial negative CK and troponin levels and cannot therefore account for the elevated hs-CRP levels.

The level of CRP did not correlate with the severity of CAD, as subjects with and without significant CAD had similar CRP levels. This is not unanticipated since the majority of MIs occur in patients with non-flow-limiting stenoses of the coronary vessels. It suggests, however, that intrinsic abnormalities in the endothelium (as reflected by the elevated CRP levels) predispose to an adverse outcome.

An ethnic difference in CAD and MI in the Singapore population has been documented with Indians having both the highest incidence of CAD and MI.[20,21] A striking finding was the observation that Indian subjects had higher CRP levels when compared to other ethnicities. These significant differences in a small country state with a stable economy and freely accessible healthcare system suggest the overwhelming role of other factors. Whether this

difference in CRP level can be attributed to genetic differences remains uncertain and further work will provide insight.

Several limitations exist in our study. This is a prospective but non-randomised registry of patients presenting to a tertiary hospital. Only 347 patients were recruited with a predominance of Indians compared to the general population.[22] However, we have no reason to believe that our study cohort does not represent the general population of patients admitted for evaluation of chest pain complaints because previous studies have shown a similar higher prevalence of CAD among Indians compared to the other races.[20,21] Quantification of coronary angiographic findings was limited to visual interpretation by the attending cardiologist but this is representative of "real-world" practice. It is well documented that patients with cardiac failure had a poor prognosis.[23] Although we did not quantify the left ventricular ejection fraction, we excluded all patients with clinical or radiological evidence of left or right ventricular failure at presentation. Because of the small number of individual events, a composite endpoint was employed. This, however, is similar to that used in currently published studies evaluating the prognostic value of CRP. Our study is consistent with current published data on the value of an elevated CRP in the prediction of an adverse cardiac event. However, whether CRP is an innocent bystander or contributes to the pathogenesis of atherosclerosis remains to be determined.

The importance of CRP measurement lies in its additive predictive value. In a heterogenous group of high-risk patients presenting with chest pain complaints and proceeding to coronary angiography, an elevated CRP level may warrant closer monitoring and possibly more aggressive intervention. Interestingly, the elevated CRP levels among Indians may reflect an intrinsic genetic predisposition. Knowledge of an elevated CRP level could also serve as an incentive to the at-risk individual to adopt life-style measures. Weight-reduction and exercise are known to lower the CRP as is statin therapy. Like cholesterol level, CRP level is inexpensively and easily measured, but is not affected by food intake and does not vary during the course of the day.

Conclusions

Based on our findings, we suggest that hs-CRP measurement may be used to further risk-stratify troponin negative high-risk patients admitted for evaluation of chest pain complaint. Additionally, the current cut-point for low risk has an acceptable predictive value in our multi-ethnic Asian population. Patients with elevated hs-CRP levels should be followed up closely and aggressive control of associated risk factors may be useful.

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REFERENCES

1. Lee TH, Goldman L. Evaluation of the patient with acute chest pain. N Engl J Med 2000;342:1187-95.
2. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med 1999;340:115-26.
3. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.
4. Koukkunen H, Penttila K, Kemppainen A, Halinen M, Penttila I, Rantanen T, et al. C-reactive protein, fibrinogen, interleukin-6 and tumour necrosis factor-alpha in the prognostic classification of unstable angina pectoris. Ann Med 2001;33:37-47.
5. Rebuzzi AG, Quaranta G, Liuzzo G, Caligiuri G, Lanza GA, Gallimore JR, et al. Incremental prognostic value of serum levels of troponin T and C-reactive protein on admission in patients with unstable angina pectoris. Am J Cardiol 1998;82:715-9.
6. Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet 1997;349:462-6.
7. Bazzino O, Ferreiros ER, Pizarro R, Corrado G. C-reactive protein and the stress tests for the risk stratification of patients recovering from unstable angina pectoris. Am J Cardiol 2001;87:1235-9.
8. Zebrack JS, Anderson JL, Maycock CA, Horne BD, Bair TL, Muhlestein JB. Usefulness of high-sensitivity C-reactive protein in predicting long-term risk of death or acute myocardial infarction in patients with unstable or stable angina pectoris or acute myocardial infarction. Am J Cardiol 2002;89:145-9.
9. Zebrack JS, Muhlestein JB, Horne BD, Anderson JL. C-reactive protein and angiographic coronary artery disease: independent and additive predictors of risk in subjects with angina. J Am Coll Cardiol 2002;39:632-7.
10. Hoffmeister HM, Ehlers R, Buttcher E, Kazmaier S, Szabo S, Beyer ME, et al. Comparison of C-reactive protein and terminal complement complex in patients with unstable angina pectoris versus stable angina pectoris. Am J Cardiol 2002;89:909-12.
11. Veselka J, Prochazkova S, Duchonova R, Bolomova I, Urbanova T, Tesar D, et al. Relationship of C-reactive protein to presence and severity of coronary atherosclerosis in patients with stable angina pectoris or a pathological exercise test. Coron Artery Dis 2002;13:151-4.
12. Magadle R, Weiner P, Beckerman M, Berar-Yanay N. C-reactive protein as a marker for active coronary artery disease in patients with chest pain in the emergency room. Clin Cardiol 2002;25:456-60.
13. Oltrona L, Ardissino D, Merlini PA, Spinola A, Chiodo F, Pezzano A. C-reactive protein elevation and early outcome in patients with unstable angina pectoris. Am J Cardiol 1997;80:1002-6.
14. Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, et al. Elevated levels of interleukin-6 in unstable angina. Circulation 1996;94:874-7.
15. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a

TIMI 11A substudy. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol 1998;31:1460-5.
16. de Winter RJ, Bholasingh R, Lijmer JG, Koster RW, Gorgels JP, Schouten Y, et al. Independent prognostic value of C-reactive protein and troponin I in patients with unstable angina or non-Q-wave myocardial infarction. Cardiovasc Res 1999;42:240-5.
17. Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. J Am Coll Cardiol 2000;35:1535-42.
18. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med 2000;343:1139-47.
19. de Winter RJ, Fischer J, Bholasingh R, van Straalen JP, de Jong T, Tijssen JG, et al. C-Reactive protein and cardiac troponin T in risk stratification: differences in optimal timing of tests early after the onset of chest pain. Clin Chem 2000;46:1597-603.
20. Lee J, Heng D, Chia KS, Chew SK, Tan BY, Hughes K. Risk factors and incident coronary heart disease in Chinese, Malay and Asian Indian males: the Singapore Cardiovascular Cohort Study. Int J Epidemiol 2001;30:983-8.
21. Mak KH, Chia KS, Kark JD, Chua T, Tan C, Foong BH, et al. Ethnic differences in acute myocardial infarction in Singapore. Eur Heart J 2003;24:151-60.
22. Singapore Census 2000 Handbook. Singapore: Department of Statistics, 2001.
23. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A-13A.